REMARKS

I. Status of the Claims

Claims 1, 5 and 7 are amended.

Claims 16-37 are withdrawn.

Claim 2 and 6 are canceled.

Claims 1, 3-15 are under prosecution.

Applicant thanks the examiner for withdrawing some rejections.

II. The Invention and Support for Amendments

As stated in the specification:

> [00036] Monofunctional monomers such as GMA, HEMA and bifunctional monomers such as EDMA, DHDM are used to fabricate macroporous polymer substrates suitable for microarrays. As monomers form polymers during radical polymerization, polymers become insoluble in the reaction medium in the presence of a thermodynamically poor solvent (porogen) and precipitate to form insoluble gel-like species (nuclei). Further polymerization proceeds both in solution and within swollen nuclei where it is kinetically preferred because local concentration of monomers is higher in the nuclei than in solution. Growing nuclei associate in clusters that form a scaffolding-like interconnected matrix on later stages of the polymerization. The interconnected matrix gets reinforced by both inter-globular cross-linking and the capture of chains that still polymerize in the solution phase during continuing polymerization leading to the final porous polymer body. The fraction of voids (macropores) within the final porous polymer is close to the volume fraction of the porogenic solvent in the initial polymerization mix because the porogen remains trapped in the voids of the cross-linked polymer. Change in the nature and concentration of initial monomers, porogen, reaction temperature, and initiator of a radical polymerization allows production of polymer structures with a wide variety of average pore size (1-1000 nm) and physico-chemical properties such as transparency, hydrophilicity, and density. This allows control of polymer size to enable custom fabrication of substrates for microarrays designed to analyze complex biological molecules, *e.g.* proteins having a

molecular weight of 150 kDa are analyzed with the macroporous polymer substrate.

III. Barany (U.S. Pat. 6,506,594) Does Not Anticipate Claims 1, 3-9, 14 and 15

Barany is directed towards detecting nucleic acid sequence differences using ligase detection with microarrays. The examiner cites to Col. 10, lines 63-64; and Col. 21, lines 40-48, but those citations only state "porous surface", which Barany uses in reference to e.g., glass supports. Nor is there any description or enablement of "porous". There is no evidence the substrate of Barany is macroporous. There is no mention of "macropores". The disclosure is so vague and general with lots of "laundry lists" that it could cover all polymers, so it not enabling nor does it satisfy the written description requirement. Col. 26, lines 40-65 do not disclose a porogenic solvent as in the pending claims. There is no teaching in Barany to use macroporous polymers as in the present claims, to enhance accessibility of specific biomolecules to a microchip.

"Macroporous" with reference to polymers, and "porogenic solvents" are terms known to those of skill in the art. In the specification, macropores is defined as having "interstitial voids sufficient to accommodate large molecules such as proteins, DNA, RNA, peptides and antibodies."

Applicant also offers definitions from publications in the art, to support its argument:

Svec and Fréchet (1995), incorporated by reference in the patent application, relate in the abstract of their paper:

> polymerization...using a mixture of monomers, porogenic solvent and free radical initiators under conditions that afford macroporous objects with extremely large channels...

and further on page 707:

> Pores with a diameter of less than 2nm are classified as micropores, pores ranging from 2 to 50 nm are mesopores, while pores over 50 nm are macropores.
>
> The pores in the macroporous polymer actually consist of the irregular voids located between clusters of the globules (macropores), or even within the globules themselves (micropores). The pore size distribution reflects the internal organization of both the globules and their clusters within the macroporous polymer and largely depends on the composition of

> the polymerization mixture and the reaction conditions. The most effective variables that control pore size distribution are the percentage of cross-linking monomer, the type and amount of porogen, the concentration of the free-radical initiator in the polymerization mixture, and the reaction temperature.

Those of skill in the art will know how to determine pore sizes (e.g., by mercury porosimetry as discussed in Svec and in Horak et al. 1993) and to modify ratios of components and reaction conditions in accord with the teachings of the present specification, for use in microchips for specific biomolecules.

Polymeric porogens are also described by Horak et al. (1993). In particular, these authors evaluated the effect of a polymeric porogen, consisting of various concentrated solutions of PMMA or PS in toluene…

In the Office Action mailed September 22, 2005 for 10/272,152, the examiner described Barany (U.S. Pat. No. 6,852,487 B1) as follows:

> Barancy teaches a porous surface that is (i.e. resin or membrane) a hydrophobic polymer (i.e. polyacrylamide) composed of combination of acrylamide with functional monomers containing carboxylate..wherein the functional monomer is acrylic acid.

It is clear that Barany does not teach substrates **in which** biomolecules are embedded as in the present claims but rather substrates **on which** oligonucleotides are attached. The substrate of Barany "and its surface preferably form a rigid support **on which** to carry out the reactions described herein… I**n a preferred embodiment, the substrate is flat glass or single-crystal silicon.** Barany, Col. 24,lines 17-40 *(emphasis added).*

The examiner rejected the previous arguments that Barany does not anticipate due to lack of enablement as "arguments of counsel." Because a RCE is now filed, applicant requests an interview to determine whether submission of a Declaration explaining why Barany does not enable all claim elements, would be helpful to overcome remaining rejections.

IV. Chang (U.S. Pat. 6,994,964) Does Not Anticipate Claims 1-3, 9 and 12-15.

Claims are amended to include limitations found in the specification supporting the distinction of "macroporous" from Chang's teaching.

Chang combined microarrays and polymer brushes and immobilization of biomolecules on polymer brushes. He utilized well-known polymer brushes and well-known immobilizations on polymer brushes to produce microarrays.

Chang uses procedures of making polymer brushes – i.e. the method to produce polymer substrates is very different from what is described in the present application. Polymer brushes described in Chang's patent are initiated by surface polymerization and results in submicron polymer thickness.

Polymer brushes are well-known. Books are written about polymer brushes. Many material exists about immobilization of biomolecules on polymer brushes.

"A 'polymeric brush' ordinarily refers to polymer films comprising chains of polymers that are attached to the surface of a substrate. The polymeric brushes of this invention are functionalized polymer films which comprise functional groups such as hydroxyl, amino, carboxyl, thiol, amide, cyanate, thiocyanate, isocyanate and isothio cyanate groups, or a combination thereof, on the polymer chains at one or more locations. The polymeric brushes of this invention are capable of attachment or stepwise synthesis of macromolecules thereon."

From Example 1 of Chang's Patent: "The AIBN-APS-silanized substrate is subjected to radical polymerization. The substrate is immersed in a 20-50% solution of 2-hydroxy ethylmethacrylate (HEMA) in degassed DMF for various reaction times and temperatures. At a reaction temperature of 70°C, the surface AIBN molecule dissociated into two radicals, initiating polymerization to form hydroxyl-functionalized methacrylate polymer. The substrates were then washed thoroughly with DMF and water, and thoroughly dried. The resulting film thickness on silicon is monitored by ellipsometry or AFJ (atomic force microscopy). For example, a range of 5-30 nm thick pHEMA film is obtained after a 24-hour polymerization."

To produce brushes, one compound immobilizes on a surface that contain initiators of the polymerization. Then this surface is immersed in some solution containing monomers, and, under some conditions (e.g. temperature) the immobilized initiator produces radicals and brushes start to grow.

In contrast, in the present application, monomer solutions (containing initiators) are applied between two surfaces (slide and mark with spacers>10 microns), and then

photopolymerization is initiated throughout the whole bulk solution between these two surfaces. Thus, "thick" block are produced, not "thin" brushes as in Chang.

In the present application, block copolymerization is used, as those of skill in the art would recognize.

V. A Prima Facie Case Of Obviousness Is Not Established.

Claims 10 and 11 were rejected under 35 USC §103 over Chang and Huang.

The examiner admits that Chang "does not teach the solvents are aromatic alcohols, e.g. cyclahexone." (Action, page 7). The examiner relies for this omission on Huang for teaching organic solvents in methacrylate polymerization and decides these are "functional equivalents." However, this is an unsupported conclusion and there is no evidence of suggestion or motivation to combine Chang and Huang. Even if combined, they do not include all the elements of claims 10 and 11.

In the present application, derivatization is achieved by incorporation of vinyl monomers that react after polymerization with some of the chemical groups from the biomolecules to form covalent bonds. (Specifically see [00037]). As shown in FIGs. 6 and 7, microchips (biochips) of the present invention have improved binding efficiency compared to commercially available biochips.

With regard to Huang, as stated in the specification about covalent bonds:

> [00037] However, in order to use the above-described macroporous polymer substrates for biochip fabrication, they should be derivatized with chemically-reactive groups specific for chemical groups that are present in biological molecules to be immobilized on a biochip (*e.g.*, amino groups, carboxylic groups). This derivatization is achieved by incorporation of vinyl monomers that react after polymerization with some of the chemical groups from biomolecules to form covalent bonds. The derivatization is also achieved after polymerization, by incorporation of vinyl monomers with chemical groups that are converted to some other chemical groups that with the chemical groups from the biomolecules to form covalent bonds.

Also arguing against obviousness is the improved performance for microchips demonstrated by compositions and methods of the present invention:

FIG. 4 shows that both substrates 1 (GMA-EDMA with compound I) and 2 (GMA-EDMA without compounds I, II or III) show higher hybridization signals that using acrylanide with III alone. (see also Example 10).

FIG. 5 shows better performance of GMA-DHDM substrates of the present invention, compared with 2 commercially available substrates. (see also Example 11 and 18)

FIG. 7 shows improved probe detection using GMA-DHDM or GMA-EDMA compared to 2 commercially available substrates. (see also Example 19).

"To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." MPEP § 706.02(j) *quoting Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). A determination of obviousness requires that "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *KSR International Co. v. Teleflex, Inc.*, -- U.S. --, 127 S.Ct. 1727, 1734, 82 U.S.P.Q.2d 1385 (2007) *quoting Graham v. John Deer Co.*, 383 U.S. 1, 17 (1966). In making a determination of obviousness by looking at the teachings of multiple patents, one should consider

> the effects of demands known to the design community or present in the market place; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit.

KSR, 127 S.Ct. at 1740-41 *(emphasis added)*. "[A] patent composed of several elements is not proved obvious merely by demonstrating the each of its elements was, independently, known in the prior art." *Id.* at 1741.

VI. Conclusion

If there are any remaining issues, the applicants' representative requests an interview prior to issuing an Office Action.

Applicants request allowance of the pending claims. No fees are believed due at this time, however, please charge any additional deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (21416-93965).

Respectfully submitted,

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